General

Guideline Title

Guidelines for the diagnosis and management of multiple myeloma 2013.

Bibliographic Source(s)

Bird JM, Owen RG, D'Sa S, Snowden JA, Pratt G, Ashcroft J, Yong K, Cook G, Feyler S, Davies F, Morgan G, Cavenagh J, Low E, Behrens J, Jenner M, Haemato-oncology Task Force of the British Committee for Standards in Haematology (BCSH), UK Myeloma Forum. Guidelines for the diagnosis and management of multiple myeloma 2013. London (UK): British Committee for Standards in Haematology (BCSH); 2013. 99 p. [278 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Smith A, Wisloff F, Samson D, UK Myeloma Forum, Nordic Myeloma Study Group, British Committee for Standards in Haematology. Guidelines on the diagnosis and management of multiple myeloma 2005. Br J Haematol. 2006 Feb;132(4):410-51.

Recommendations

Major Recommendations

Definitions for the quality of the evidence (A–C) and strength of recommendations (strong [grade 1], weak [grade 2]) are given at the end of the "Major Recommendations" field.

Diagnosis, Prognostic Factors and Disease Monitoring

Diagnostic Criteria and Differential Diagnosis

- International Myeloma Working Group (IMWG) diagnostic criteria should be used (Grade A1).
- Investigation should be based on the tests shown in the Table below including an assessment of possible myeloma-related organ and tissue impairment (ROTI) (Grade A1).
- All diagnoses should be made or reviewed by an appropriately constituted multidisciplinary team (MDT) (Grade A1).
- Plasma cell phenotyping by flow cytometry and/or immunohistochemistry on trephine biopsy sections is recommended in all cases (Grade A1).

Table. Initial Investigations in Patients with Myeloma

Screening Tests	Tests to Establish Diagnosis	Tests to Estimate Tumour Burden and Prognosis	Tests to Assess Myeloma-related Organ Impairment	Special Tests Indicated in Some Patients
FBC, ESR or plasma viscosity	Bone marrow aspirate + trephine biopsy with plasma cell phenotyping	FISH analysis	FBC	
Urea, creatinine, calcium, albumin	Immunofixation of serum and urine	Quantification of monoclonal protein in serum and urine	Serum urea and creatinine	SFLC assay in oligo-secretory, light chain only and non-secretory disease
Electrophoresis of serum and concentrated urine			Creatinine clearance (measured or calculated)	
Quantification of non-isotypic immunoglobulin		• Albumin • β2-microglobulin	• Calcium • Albumin • Plasma viscosity • Tissue biopsy (or fat pad aspirate) for amyloid (if suspected) • Quantification of non-isotypic immunoglobulins	
X-ray of symptomatic areas	Skeletal survey	Skeletal survey	Skeletal survey	• MRI • CT scan

Abbreviations: FBC, full blood count; ESR, erythrocyte sedimentation rate; FISH, fluorescence in situ hybridization; SFLC, serum-free light chain; MRI, magnetic resonance imaging; CT, computerized tomography

Monitoring and Indications for Starting Therapy

- Chemotherapy is only indicated in patients with symptomatic myeloma based on the presence of ROTI (Grade C2).
- Patients with asymptomatic myeloma should be monitored under the supervision of a Consultant Haematologist. These patients should be offered entry into clinical trials if available (Grade A1).
- Monitoring of patients with asymptomatic myeloma should include regular (typically 3-monthly) clinical assessment for the emergence of ROTI and measurement of serum and urinary M-protein (and serum-free light chain [SFLC] when indicated). Repeat bone marrow (BM) examination and skeletal imaging should be considered prior to the start of treatment (Grade A1).

Prognostic Factors and Staging in Symptomatic Myeloma

- The International Staging System (ISS) based on serum albumin and β2-microglobulin should be used (Grade C1).
- Fluorescence in situ hybridization (FISH) studies are recommended for all patients at diagnosis as they provide important prognostic information but their role in directing therapy needs further evaluation in prospective clinical trials (Grade C1).
- Newer techniques for prognostic assessment should continue to be utilised in the context of clinical trials to evaluate future incorporation in to routine clinical practice (Grade C1).

Measuring Response to Therapy

- Response to therapy should be defined using the IMWG uniform response criteria (Grade B1).
- The response category stringent complete response (sCR) is recommended only for use in the clinical trial setting (Grade B1).
- The SFLC assay should be used to assess response in all patients with light chain only, non-secretory and oligosecretory disease (Grade B1).

Imaging Techniques

- The skeletal survey remains the screening technique of choice at diagnosis (Grade B1).
- The skeletal survey should include a postero-anterior (PA) view of the chest, antero-posterior (AP) and lateral views of the cervical spine, thoracic spine, lumbar spine, humeri and femora, AP and lateral view of the skull and AP view of the pelvis; other symptomatic areas should

be specifically visualized with appropriate views (Grade B1).

- Computerized tomography (CT) scanning or magnetic resonance imaging (MRI) should be used to clarify the significance of ambiguous plain radiographic findings, such as equivocal lytic lesions, especially in parts of the skeleton that are difficult to visualize on plain radiographs, such as ribs, sternum and scapulae (Grade A1).
- Urgent MRI is the diagnostic procedure of choice to assess suspected cord compression in myeloma patients with or without vertebral collapse. Urgent CT scanning is an alternative, when MRI is unavailable, intolerable or contraindicated.
- CT or MRI is indicated to delineate the nature and extent of soft tissue masses and where appropriate, tissue biopsy may be guided by CT scanning (Grade A1).
- There is insufficient evidence to recommend the routine use of positron-emission tomography (PET) or ^{99m}technetium sestamibi (MIBI) imaging. Either technique may be useful in selected cases for clarification of previous imaging findings preferably within the context of a clinical trial (Grade C2).
- Bone scintigraphy has no place in the routine staging of myeloma (Grade A1).
- Routine assessment of bone mineral density cannot be recommended, owing to the methodological difficulties of the technique and the universal use of bisphosphonates in all symptomatic myeloma patients (Grade A1).

Management of Common Medical Emergencies in Myeloma Patients

Hyperviscosity

- Symptomatic hyperviscosity should be treated with therapeutic plasma exchange with saline fluid replacement (Grade A1).
- If plasmapheresis is not immediately available but hyperviscosity symptoms are present, consider isovolaemic venesection with saline replacement as a holding measure (Grade A1).
- Effective treatment of the underlying disease should be started as soon as possible (Grade A1).

Hypercalcaemia

- In mild hypercalcaemia (corrected calcium 2.6–2.9 mmol/l) re-hydrate with oral and/or intravenous (IV) fluids (Grade A1).
- In moderate-severe hypercalcaemia (corrected calcium >2.9 mmol/l) re-hydrate with IV fluids and give furosemide if required (Grade B1).
- Zoledronic acid is the bisphosphonate of choice in the treatment of hypercalcaemia (Grade B1).

Cord Compression

- Urgent MRI should be performed and neurosurgical or spinal surgical/clinical oncology consultation obtained (Grade A1).
- Local radiotherapy is the treatment of choice for non-bony lesions and should be commenced as soon as is possible, preferably within 24 h of diagnosis. A dose of 30 Gy in 10 fractions is recommended (Grade B1).
- Surgery is recommended for emergency decompression in the setting of bony compression and/or to stabilize the spine (Grade A1).
- If cord compression is a presenting symptom, it is important to concurrently pursue a rapid diagnosis and to institute systemic therapy as soon as possible (Grade A1).

Early Infection

- There must be 24-h access to specialist advice for the patient and/or primary care team (Grade A1).
- Any febrile myeloma patient should be treated promptly with broad-spectrum antibiotics. IV antibiotics are required for severe systemic infection or neutropenic sepsis (Grade A1).
- Aminoglycosides should be avoided, if possible (Grade B2).
- There is insufficient evidence to recommend the routine use of prophylactic antibiotics (Grade C2).

Myeloma Bone Disease

Bone Fractures

- Local radiotherapy is helpful for pain control; a dose of 8 Gy single fraction is recommended (Grade B1).
- Long bone fractures require stabilization and subsequent radiotherapy; a dose of 8 Gy single fraction is recommended (Grade B1).

Bisphosphonates

- Bisphosphonate therapy is recommended for all patients with symptomatic multiple myeloma, whether or not bone lesions are evident (Grade A1).
- Zoledronic acid and pamidronate both show efficacy with respect to skeletal-related event (SRE) prevention but early data regarding

prolongation of event-free survival (EFS) and overall survival (OS) in a large randomized trial suggest that zoledronic acid should be the bisphosphonate of choice (Grade B1).
- Sodium clodronate is less effective than zoledronic acid but has a significantly lower incidence of bisphosphonate-associated osteonecrosis of the jaw (BONJ) (Grade B1).
- There is no consensus regarding the duration of bisphosphonate therapy. The standard of care to date has been indefinite bisphosphonate therapy. However, given the risk of BONJ, it is reasonable to consider stopping therapy under certain circumstances, such as in those patients who have achieved a complete response (CR) or very good partial response (VGPR) with transplantation and/or a novel therapy combination and have no active bone disease; this should be at the discretion of the treating haematologist. In the absence of definitive data the duration of therapy should take into account individual factors such as remission status, extent of skeletal disease, renal function and patient preference. In patients who do stop bisphosphonate therapy, therapy should be reinstituted at the time of relapse (Grade C2).
- Renal function should be carefully monitored and doses reduced in line with the manufacturers' guidance. For guidance on the use of bisphosphonates in renal impairment, see Appendix 2 in the original guideline document (Grade A1).
- At present there is insufficient evidence to make a recommendation for the use of bisphosphonates in patients with asymptomatic myeloma (Grade C2).
- Dental evaluation should be carried out before starting IV bisphosphonate therapy (Grade A1).

Renal Impairment

Early Management of Renal Failure

- Vigorously rehydrate with at least 3 litres of normal saline daily (Grade A1).
- Treat precipitating events (e.g., hypercalcaemia, sepsis and hyperuricaemia) and discontinue nephrotoxic drugs, particularly non-steroidal anti-inflammatory drugs (NSAIDs) (Grade A1).
- Consider physical methods of removing free light chains from the blood (plasma exchange, large pore haemofiltration) within the context of a clinical trial (Grade C2).
- Administer high dose dexamethasone unless otherwise contraindicated pending initiation of definitive treatment which should be started without delay.
- Monitor SFLC levels (Grade B1).
- Identify and treat infection vigorously (Grade A1).
- Patients with renal failure require dose modification of bisphosphonates and the risk of renal adverse events may be greater in patients with impaired renal function. For guidance on use of bisphosphonates in patients with renal impairment, see Appendix 2 of the original guideline document (Grade A1).

Induction Therapy Including Management of Major Toxicities and Stem Cell Harvesting

Initial Treatment When High Dose Therapy (HDT) Is Not Planned

General

- Chemotherapy prescription should be undertaken by an experienced clinician with input from a specialist chemotherapy-trained pharmacist (Grade A1).
- Summary of Product Characteristics (SPC) recommendations for dose adjustments of chemotherapy drugs and use of granulocyte colony-stimulating factor (G-CSF) support should be followed wherever possible (Grade A1).
- Patients should be appropriately dosed, to allow for renal and liver function (Grade A1).
- Patients with cytopenias at baseline due to limited marrow reserve require more frequent monitoring and dose adjustment (Grade A1).
- All patients should be considered for entry into a clinical trial (Grade A1).
- The choice of therapy should take into account patient preference, co-morbidities and toxicity profile (Grade A1).

Specific Treatment Recommendations for Induction Therapy Prior to HDT

- Vincristine, doxorubicin and dexamethasone (VAD) or single agent dexamethasone should no longer be routinely used as induction therapy (Grade A1).
- Induction regimens should contain at least one novel agent (Grade A1).
- Examples of induction regimens that are superior to VAD in terms of response rates include cyclophosphamide, thalidomide and dexamethasone (CTD), thalidomide, doxorubicin and dexamethasone (TAD), bortezomib/dexamethasone and bortezomib, doxorubicin and dexamethasone (PAD) (Grade A1).
- Decisions regarding the most appropriate induction for individual patients will require the assessment of a number of factors, such as renal

function, thrombotic risk and pre-existing neuropathy although it is appreciated that some agents are not routinely funded as initial therapy in the UK. CTD is the combination of which there is the most clinical experience in the UK (Grade C2).

Specific Treatment Recommendations for Older and/or Less Fit Patients in Whom HDT Is Not Planned Initial Therapy

Induction therapy should consist of either:

- A thalidomide-containing regimen in combination with an alkylating agent and steroid such as melphalan, prednisolone and thalidomide (MPT) or cyclophosphamide, thalidomide and dexamethasone in attenuated doses (CTDa) (Grade C2) or
- Bortezomib in combination with melphalan and prednisolone (Grade C1)

Specific Treatment Recommendations for Patients with Plasma Cell Leukaemia and Rarer Myeloma Subtypes

- The use of initial treatment with bortezomib and autologous stem cell transplantation should be considered in responding patients with plasma cell leukaemia (Grade C1).
- Immunoglobulin D (IgD), immunoglobulin E (IgE) and immunoglobulin M (IgM) myeloma are associated with a poor outcome but there is insufficient data to support specific alternative treatment strategies at this time (Grade C1).

Prevention and Management of Treatment Related Complications of Therapy

Peripheral Neuropathy

The investigation and management of peripheral neuropathy is described in detail in the British Committee for Standards in Haematology Guidelines for supportive care in multiple myeloma 2011 . Some of the key recommendations are listed below:

- Peripheral neuropathy is common at diagnosis and as a result of many myeloma therapies.
- Peripheral neuropathy and autonomic neuropathy symptoms and signs should be actively sought and sequentially graded during the course of therapy using a scale, such as the National Cancer Institute Common Toxicity Criteria to provide an objective assessment and allow identification of trends (Grade A1).
- Any patient who develops a significant (e.g., >National Cancer Institute [NCI] Grade 2) or progressive peripheral or autonomic neuropathy following treatment should be managed with graded dose reduction or drug withdrawal. Guidelines for dose reductions of thalidomide and bortezomib are shown in Table 11 in the original guideline document. Continuation of dose intense treatment in the face of neuropathy may cause permanent neurological damage (Grade A1).
- The management of peripheral neuropathy should include symptom control along with treatment of any potentially reversible causes. Optimal management of co-morbid causes such as diabetes mellitus may also improve tolerance of neurotoxic drugs (Grade A1).
- Neuropathic pain is poorly responsive to simple analgesics, NSAIDs and opioid drugs. Neuromodulatory agents are being increasingly recommended to treat neuropathic pain. Patients with progressive neuropathic pain despite appropriate analgesia should be referred promptly for specialist advice regarding pain management (Grade A1).

Thromboprophylaxis

- Cancer, cancer therapies, infection, previous venous thromboembolism (VTE), immobility, obesity, paraplegia, erythropoietin treatment, dehydration and renal failure are all well-recognized risk factors for VTE, particularly in hospitalized patients. As with other areas of thromboprophylaxis, a risk stratified approach is appropriate in patients with myeloma (Grade A1).
- A risk assessment model for the prevention of VTE in multiple myeloma patients treated with thalidomide or lenalidomide is contained within the Guidelines for supportive care in multiple myeloma 2011 .
- All patients who are due to start thalidomide or lenalidomide-containing therapy should undergo a risk assessment for VTE and prospectively receive appropriate thromboprophylactic measures (Grade A1).
- In patients receiving thalidomide or lenalidomide, aspirin 75–325 mg may be considered as VTE prophylaxis in low risk patients only (i.e., without risk factor present), unless contraindicated (Grade B2).
- Patients receiving thalidomide or lenalidomide in addition to combination chemotherapy/anthracyclines/high dose steroids, or those with two or more myeloma/individual risk factors should be offered prophylaxis with low-molecular-weight heparin (LMWH) (high-risk prophylactic dose) or dose-adjusted therapeutic warfarin, unless contraindicated. There is no role for fixed, low dose warfarin (Grade B1).
- The duration of thromboprophylaxis remains unclear but should be guided by risk factors such as active disease (e.g., for the first 4–6 months of treatment until disease control achieved) and de-escalated or discontinued unless there are ongoing significant risk factors (Grade C2).
- Treatment of confirmed VTE should follow current practice guidelines using adjusted dose warfarin or LMWH and appropriate monitoring (Grade A1).

Can Novel Agents Overcome the Poor Prognosis Associated with Adverse Cytogenetic Abnormalities?

- Novel agents have increased the overall and complete remission rates if used pre-autologous stem cell transplantation (ASCT) (Grade A1).
- Confirmation is needed that these higher response rates translate into longer progression-free survival (PFS) and overall survival (OS) after ASCT (Grade C2).
- Further data regarding a number of combinations are required, particularly those containing more than 1 novel agent (Grade C2).

Stem Cell Harvesting After Induction Therapy Including Novel Agents

Stem Cell Mobilization

- Peripheral blood stem cell harvesting (PBSCH) should be carried out within 4 to 6 cycles for all induction regimens that incorporate a novel agent (Grade B1).
- If induction therapy with a lenalidomide-containing regimen has continued for >4 cycles, mobilization with cyclophosphamide and G-CSF is recommended (Grade C2).
- Ideally patients should undergo stem cell mobilization within 6 to 8 weeks of completion of induction therapy (Grade B1).

Chemotherapy in Patients with Renal Failure

- Dexamethasone alone can be given as initial treatment pending decisions on subsequent chemotherapy and the outcome of full supportive measures (Grade B1).
- Melphalan can be considered for patients with renal impairment in whom other regimens may be relatively contraindicated. The dose should be reduced by 25% in the first course if glomerular filtration rate (GFR) <30 ml/min and titrated against marrow toxicity in subsequent courses (Grade C2).
- Cyclophosphamide can be used with a dose reduction of 25% if the GFR is 10–50 ml/min, and of 50% if GFR is <10 ml/min and titrated in subsequent courses according to response (Grade A1).
- Thalidomide can be used without dose modification in patients with renal failure (Grade A1).
- Bortezomib can be safely used in myeloma patients with renal failure including those on dialysis at the standard starting dose of 1.3 mg/m^2. However, because of limited data on toxicity, patients with renal impairment (creatinine clearance ≤30 ml/min) and patients on haemodialysis should be closely monitored for toxicity. Although there is mounting evidence that bortezomib appears effective in this setting, further studies are needed to confirm results derived from subgroup analyses of large randomized trials and data from other non-randomized studies (Grade A1).
- Lenalidomide can be given in patients with renal impairment but dose adjustments as recommended by the manufacturer should be implemented (Grade A1).

<u>Myeloma Refractory to Induction Therapy</u>

- All patients should be considered for entry into a clinical trial (Grade A1).
- For patients intolerant of thalidomide, or refractory to first-line therapy, a bortezomib-based salvage regimen is recommended (Grade B2).
- Patients with ≥Grade 2 peripheral neuropathy should receive a lenalidomide-based regimen (Grade B1).

<u>HDT and ASCT</u>

HDT in Renal Failure

- HDT with ASCT should be part of primary treatment in newly diagnosed patients up to the age of 65 years with adequate performance status and organ function (Grade C1).
- HDT with ASCT should be considered in patients aged >65 years with good performance status (Grade C1).
- Conditioning with melphalan alone, without total body irradiation (TBI), is recommended (Grade B1). The usual dose is 200 mg/m^2 but this should be reduced in older patients (>65–70 years) and those with renal failure.
- Planned double ("tandem") ASCT cannot be recommended on the current evidence. However, it is recommended that enough stem cells are collected to support two high dose procedures in patients with good performance status (Grade B1).
- Purging is not of clinical benefit and is not therefore recommended (Grade C1).
- HDT and ASCT may be considered for patients with severe renal impairment (creatinine clearance/GFR <30 ml/min) but the dose of melphalan should be reduced to a maximum of 140 mg/m^2 (Grade B2) and the procedure should only be carried out in a centre with special expertise and specialist nephrology support (Grade C1).

<u>Allogeneic Stem Cell Transplantation (AlloSCT)</u>

- Treatment decisions that involve AlloSCT are some of the most difficult for patients. Patients need to be fully informed and involved in the decision making process. Young patients with matched sibling donors who are interested in pursuing curative therapy should be referred to a haematologist with an interest in allografting myeloma patients so that they gain an understanding of the risks and benefits of this procedure (Grade C2).
- AlloSCT should be carried out in European Group for Blood and Bone Marrow Transplant (EBMT) accredited centres where data are collected prospectively as part of international transplant registries and, where possible, should be carried out in the context of a clinical trial (Grade A1).
- Allogeneic transplant procedures for patients with myeloma in first response should only be considered for selected groups because of the risk of significant transplant-related morbidity and mortality (Grade C2).
- A myeloablative matched family donor (MFD) AlloSCT should only be considered in selected patients up to the age of 40 years who have achieved at least a partial response to initial therapy (Grade C2).
- A myeloablative matched unrelated donor (MUD) AlloSCT is not recommended except in the context of a clinical trial (Grade C2).
- A reduced intensity conditioned (RIC) MFD or MUD AlloSCT is a clinical option for selected patients preferably in the context of a clinical trial. If carried out, RIC AlloSCT should generally be performed following an autograft, early in the disease course in patients with responsive disease (Grade C2).
- Donor lymphocyte infusions (DLI) should be considered for patients with persistent or progressive disease following transplantation or for mixed chimerism. If given for disease progression, cytoreduction should probably be carried out first (Grade C2). Effective doses of DLI are associated with a significant risk of graft versus host disease (GVHD).

Maintenance Therapy

- Interferon (IFN)-α or single-agent corticosteroids cannot be routinely recommended as maintenance therapy. (Grade A) In the allograft setting, IFN-α may be useful for patients who have not achieved a CR (Grade C2).
- Maintenance with single agent thalidomide therapy may improve EFS and OS in patients who did not achieve VGPR post high-dose therapy and in this setting maintenance therapy could be considered (Grade C2). Patients with deletion 13q may not benefit (Grade C2).
- The dose of thalidomide should not exceed 150 mg and no recommendation can be made with regards to the duration of thalidomide maintenance (Grade C2).
- In the maintenance setting, routine anticoagulant prophylaxis is not required (Grade B1).
- At present, there is no evidence of benefit for the use of thalidomide maintenance in elderly patients who did not undergo autologous transplantation (Grade C2).
- The combination of steroids and thalidomide is not recommended in the maintenance setting due to increase toxicity and unclear benefit over thalidomide alone (Grade B1).
- Although promising data are emerging for the use of bortezomib or lenalidomide in the maintenance setting, long term published data are still awaited to be able to recommend their use outside clinical trials (Grade C2).

Management of Relapsed Myeloma Including Drugs in Development

Choice of Treatment at Relapse

- The most appropriate management should be determined on an individual basis depending on the timing of relapse, age, prior therapy, BM function and co-morbidities, and patient preference (Grade A1).
- Extensive trial data support the use of thalidomide, bortezomib and lenalidomide-based regimens as treatment modalities at first and subsequent relapse (Grade A1).
- Clinical effectiveness of thalidomide, bortezomib and lenalidomide is not dependent on the number of previous lines of therapy, or type of therapy previously received (Grade C2).
- Unless contraindicated, treatment with thalidomide, bortezomib or lenalidomide treatment should be delivered with dexamethasone +/- chemotherapy to increase the response rate (Grade A1).
- A second ASCT may be considered in patients who had a good response to the initial transplant procedure (≥18 months to disease progression) (Grade B1).
- Where possible, patients should be treated in the context of a clinical trial. Phase I/II trials are appropriate for patients with relapsed/refractory myeloma (Grade A1).
- Good supportive therapy is essential (Grade A1).

Patient Information and Support

- The diagnosis needs to be communicated honestly to the patient and their family without delay.

- Information should be communicated in a quiet area with privacy, ideally in the company of a close relative and with the presence of a specialist nurse. The information needs of the patient's family need to be facilitated wherever possible.
- Patients and their partners/carers should be given time to ask appropriate questions once they have been given the diagnosis; this may be best be done after an interval of a few hours or days.
- Patients should be made aware of appropriate clinical studies.
- Treatment plans need to be communicated simply to the patient and his/her carer and should be clearly written in the case record so that the information is readily accessible to other members of the multi-disciplinary specialist team.
- Patients need to be informed of the names of the key members of the specialist team who are in charge of their care and given clear information on access to advice/support from the team.
- At the end of a consultation it is recommended that patients and their family/carers have written information on the condition. It should also guide patients and their family/carers on access to other information services.

Definitions:

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Multiple myeloma

Guideline Category

Diagnosis

Management

Treatment

Clinical Specialty

Hematology

Oncology

Radiation Oncology

Radiology

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To update the 2010 British Committee on Standards in Haematology "Diagnosis and management of multiple myeloma" guideline

Target Population

Individuals with suspected or confirmed multiple myeloma

Interventions and Practices Considered

Diagnosis/Evaluation

1. Diagnosis, assessment of prognostic factors, and disease monitoring
    - Use of International Myeloma Working Group (IMWG) diagnostic criteria
    - Initial investigations
        - Screening tests
        - Tests to establish diagnosis
        - Tests to estimate tumour burden and prognosis
        - Tests to assess myeloma-related organ impairment
        - Special tests indicated in some patients
    - Multidisciplinary team involvement
    - Plasma cell phenotyping
    - Monitoring and indications for starting therapy
    - Prognostic assessment and staging in symptomatic myeloma (International Staging System)
    - Measuring response to therapy (IMWG uniform response criteria, serum-free light chain assay)
2. Imaging techniques
    - Skeletal survey
    - Magnetic resonance imaging (MRI)
    - Computerized tomography (CT) scan
    - Positron-emission tomography (PET) or ^{99m}Technetium sestamibi (MIBI) imaging (not recommended routinely)
    - Bone scintigraphy and assessment of bone mineral density (not recommended)

Management/Treatment

1. Management of common medical emergencies: hyperviscosity, hypercalcaemia, cord compression, and early infection
2. Management of myeloma bone disease
    - Local radiotherapy and stabilization for bone fractures
    - Bisphosphonate therapy with renal monitoring and dental evaluation
3. Management of renal impairment
    - Vigorous rehydration
    - Treating precipitating events and discontinuing nephrotoxic drugs
    - High-dose dexamethasone
    - Monitoring serum-free light chain (SFLC)
    - Identifying and treating infection
    - Bisphosphonate dose modification
4. Induction therapy including management of major toxicities and stem cell harvesting
    - Induction therapy including at least one novel agent: cyclophosphamide, thalidomide and dexamethasone (CTD), thalidomide, doxorubicin and dexamethasone (TAD), bortezomib/dexamethasone and bortezomib, doxorubicin and dexamethasone (PAD)
    - Specific treatment for older and/or less fit patients in whom high-dose therapy (HDT) is not planned initial therapy
    - Specific treatment for patients with plasma cell leukaemia and rarer myeloma subtypes
    - Prevention and management of treatment-related complications of therapy (peripheral neuropathy, thromboprophylaxis)
    - Use of novel agents
    - Stem cell harvesting after induction therapy including novel agents
    - Chemotherapy in patients with renal failure
5. Management of myeloma refractory to induction therapy
6. High-dose therapy and autologous stem cell transplantation (ASCT)
7. Allogeneic stem cell transplantation (AlloSCT)
8. Maintenance therapy
9. Management of relapsed myeloma including drugs in development
10. Providing patient information and support

Major Outcomes Considered

- Response to therapy (partial response rate, complete response rate)
- Survival (progression-free, event-free, overall)
- Toxicity of treatment
- Quality of life
- Treatment-related mortality

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The production of these guidelines involved review of key literature to April 2013, including the Cochrane database, Medline, internet searches and major conference reports.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Levels of evidence have been updated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature for assessing the quality of evidence and providing strength of recommendations (http://www.gradeworkinggroup.org/index.htm).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The production of these guidelines involved the following steps:

- Establishment of working groups in each of the main topic areas of the guideline
- Development of key recommendations based on randomized, controlled trial evidence. In the absence of randomized data, recommendations were developed on the basis of literature review and a consensus of expert opinion.
- involvement of patient advocacy through Myeloma UK

Grades of recommendation have been updated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature for assessing the quality of evidence and providing strength of recommendations (http://www.gradeworkinggroup.org/index.htm).

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Strong (Grade 1): Strong recommendations (Grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as "recommend".

Weak (Grade 2): Where the magnitude of benefit or not is less certain a weaker Grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as "suggest".

Cost Analysis

In preparing these guidelines the authors have considered overall cost-effectiveness of recommended interventions as well as clinical efficacy data but formal health economic assessments have not been carried out.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The production of these guidelines involved the following steps:

- Review by UK Myeloma Forum (UKMF) Executive and British Committee for Standards in Haematology (BCSH) Committees
- Review by a British Society for Haematology (BSH) sounding board

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for most of the recommendations (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Accurate diagnosis and appropriate management of multiple myeloma, including:

- Control of disease and pain
- Prevention of debilitating and life-threatening complications
- Improved quality of life
- Prolonged survival

Potential Harms

- Side effects of chemotherapy and conditioning therapy for stem cell transplantation, adverse events, treatment-related mortality
- Table 7 in the original guideline document compares side effects related to treatment with the novel agents thalidomide, bortezomib and lenalidomide. These side effects include neutropenia, thrombocytopenia, neuropathy, constipation, diarrhoea, somnolence, fatigue and thrombotic risk.
- Tables 8, 9 and 10 in the original guideline document list important toxicities related to thalidomide, bortezomib and lenalidomide.

- Appendix 2 of the original guideline document lists recommended dose reductions for various toxicities.

Qualifying Statements

Qualifying Statements

- While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the UK Myeloma Forum (UKMF), the British Society for Haematology (BSH) nor the publishers accept any legal responsibility for the content of these guidelines.
- Annual review of recommendation updates will be undertaken and any altered recommendations posted on the Web sites of the British Committee for Standards in Haematology (http://www.bcshguidelines.com/) and UKMF (http://www.ukmf.org.uk/).

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Audit Criteria/Indicators

Chart Documentation/Checklists/Forms

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Bird JM, Owen RG, D'Sa S, Snowden JA, Pratt G, Ashcroft J, Yong K, Cook G, Feyler S, Davies F, Morgan G, Cavenagh J, Low E, Behrens J, Jenner M, Haemato-oncology Task Force of the British Committee for Standards in Haematology (BCSH), UK Myeloma Forum. Guidelines for the diagnosis and management of multiple myeloma 2013. London (UK): British Committee for Standards in Haematology (BCSH); 2013. 99 p. [278 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2006 Feb (revised 2013)

Guideline Developer(s)

British Society for Haematology Guidelines - Professional Association

Source(s) of Funding

This guideline document was produced with the help of an educational grant from Myeloma UK.

Guideline Committee

Haemato-oncology Task Force of the British Committee for Standards in Haematology (BCSH), UK Myeloma Forum

Composition of Group That Authored the Guideline

Authors: Jenny M. Bird, Avon Haematology Unit, Bristol Haematology and Oncology Centre, Bristol; Roger G. Owen, Department of Haematology, Leeds Teaching Hospitals NHS Trust; Shirley D'Sa, Department of Haematology, University College Hospital, London; John A. Snowden, Department of Haematology, Sheffield Teaching Hospitals NHS Trust; Guy Pratt, Department of Haematology, Heart of England NHS Trust, Birmingham; John Ashcroft, Department of Haematology, Leeds Teaching Hospitals NHS Trust; Kwee Yong, Department of Haematology, University College Hospital, London; Gordon Cook, Department of Haematology, Leeds Teaching Hospitals NHS Trust; Sylvia Feyler, Department of Haematology, Calderdale and Huddersfield NHS Trust; Faith Davies, Haemato-oncology Unit, Royal Marsden Hospital, London; Gareth Morgan, Haemato-oncology Unit, Royal Marsden Hospital, London; Jamie Cavenagh, Department of Haematology, St. Bartholomew's Hospital, London; Eric Low, Myeloma UK, Edinburgh; Judith Behrens, Department of Haematology, St Helier Hospital, Carshalton, Surrey; Matthew Jenner, Department of Haematology, University hospital Southampton

Financial Disclosures/Conflicts of Interest

Not stated

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Smith A, Wisloff F, Samson D, UK Myeloma Forum, Nordic Myeloma Study Group, British Committee for Standards in Haematology. Guidelines on the diagnosis and management of multiple myeloma 2005. Br J Haematol. 2006 Feb;132(4):410-51.

Guideline Availability

Electronic copies: Available from the British Committee for Standards in Haematology Web site .

Print copies: Available from the British Committee for Standards in Haematology; Email: bcsh@b-s-h.org.uk.

Availability of Companion Documents

A haematology audit template is available from the British Committee for Standards in Haematology Web site .

Appendix 4 of the original guideline document contains suggested proforma for the early detection of bortezomib-associated toxicities.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI on September 25, 2006. The information was verified by the guideline developer on October 25, 2006. This summary was updated by ECRI on January 29, 2007, following the U.S. Food and Drug Administration advisory on erythropoiesis stimulating agents. This summary was updated by ECRI Institute on July 9, 2007, following the FDA advisory on erythropoiesis stimulating agents. This summary was updated by ECRI Institute on March 21, 2008 following the FDA advisory on Erythropoiesis Stimulating Agents. This summary was updated by ECRI Institute on August 15, 2008 following the U.S. Food and Drug Administration advisory on Erythropoiesis Stimulating Agents (ESAs). This summary was updated by ECRI Institute on February 26, 2010 following the U.S. Food and Drug Administration advisory on Velcade (bortezomib). This summary was updated by ECRI Institute on April 1, 2010 following the U.S. Food and Drug Administration advisory on Erythropoiesis-Stimulating Agents (ESAs). This NGC summary was updated by ECRI Institute on October 18, 2013. This summary was updated by ECRI Institute on March 7, 2014 following the U.S. Food and Drug Administration advisory on Low Molecular Weight Heparins.

Copyright Statement

Disclaimer

NGC Disclaimer

Readers with questions regarding guideline content are directed to contact the guideline developer.